AMENDED 510(k) SUMMARY OF SAFETY & EFFECTIVENESS
(Amended 11/25/03)

IDENTIFICATION INFORMATION

SUBMITTER'S INFORMATION

This summary of 510(k) safety and effectiveness is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K032222

SUBMITTER'S NAME AND ADDRESS: Meridian Bioscience, Inc.
3471 River Hills Drive
Cincinnati, OH 45244

PHONE NUMBER: (513) 271-3700

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CONTACT PERSON: Susan Rolih
Vice President, Regulatory Affairs and Quality Assurance
Official Correspondent

DATE SUMMARY PREPARED: July 18, 2003

NAME OF DEVICE: ImmunoCard STAT!® HpSA®
(ImmunoCard STAT! and HpSA are registered trademarks of Meridian Bioscience, Inc.)

COMMON NAME: Lateral flow immunoassay for *H. pylori* stool antigen

CLASSIFICATION NAME: *Campylobacter pylori* [83LYR]

REGULATION: 866.3110

PREDICATE EQUIVALENT DEVICES: Premier Platinum HpSA® (K983255)

INTENDED USE:

ImmunoCard STAT! HpSA is a rapid in vitro qualitative assay for the detection of *Helicobacter pylori* antigen (HpSA) in human stool. The stool antigen detection is intended to aid in the diagnosis of *H. pylori* infection and to demonstrate loss of *H. pylori* stool antigen following treatment. Conventional medical practice recommends that testing by any method to confirm the loss of antigen be done at least four weeks following completion of therapy. (1)

BACKGROUND:

H. pylori is a spiral gram-negative bacterium that invades the mucosal membrane of the gastrointestinal tract. It causes chronic gastritis, predisposes some infected patients to gastric and peptic duodenal ulcers. (1-3) Noninvasive in vitro diagnostic assays, such as ImmunoCard STAT! HpSA, have been shown to be effective in differentiating infected from noninfected patients. Such noninvasive assays are also recommended to

monitor the success and failure of treatment regimens to eradicate the organism. (3)

H. pylori is found in the stomachs of humans. Infections with the organism are distributed world –wide, however the preponderance appears in developing countries, where the incidence of infection is 70-80%. In developed or more industrialized countries, the incidence of infection is only 25-50%. The incidence continues to decrease in persons in higher socioeconomic levels. Infections in all groups appear to occur in childhood and many before the age of 10 years. Males and females appear to be infected at the same rates. (4) Transmission of the organism between humans is not well understood, particularly since the harbor for the infection is the human stomach. It is most likely that all infections have occurred through ingestion of fecally contaminated materials.

All infected patients develop chronic gastric inflammation but the condition is usually asymptomatic. *H. pylori* is the direct cause of most gastric and duodenal ulcers. Eradication of the organism leads to cure of the ulcers. Infection due to *H. pylori* is strongly associated with atrophic gastritis (which is a precursor to gastric cancer) and with adenocarcinoma of the distal stomach.

A variety invasive and noninvasive tests are used to detect and isolate *H pylori.* Invasive testing includes histological biopsy for hematoxylin and eosin (H and E) staining, bacterial culture, urease testing and PCR analysis. Invasive tests present some slight degree of risk for the patient due to complications. Noninvasive tests include those to monitor breath, serum, gastric juice and urine for the direct or indirect presence of organisms.

DEVICE DESCRIPTION:

ImmunoCard *STAT!* HpSA is a qualitative horizontal flow in vitro diagnostic device used to detect the presence of *H. pylori* antigen in human stool specimens. The intended use of the device is identical to that of Premier Platinum HpSA (Meridian Bioscience, Inc., Cincinnati, OH) an enzyme-linked immunoassay previously cleared to market under 510(k) K983255. While assay methods differ, both are designed to detect *Helicobacter pylori* antigen in the stools of patients. The results of both tests are intended to aid in the diagnosis of *H. pylori* infection and to monitor bacterial reduction in response to anti-bacterial therapy.

A. Technological characteristics compared to predicate device:

Characteristics	***IC STAT! HpSA***	**Premier Platinum HpSA**
Device Type		
In vitro diagnostic device	Yes	Yes
Control	No	No
Calibrator	No	No
Intended Use		
Detection of H. pylori antigens in human stool	Yes	Yes
Acceptable Sample		
Formed stool	Yes	Yes
Semi-solid stool	Yes	Yes
Liquid stool	Yes	Yes
Watery stool samples	No	No
Stool collected in transport media	No	No

Comparison of Assay Methods

Characteristic	*IC STAT! HpSA*	*Premier Platinum HpSA*
Intended use	Detection of *H. pylori* antigen in stool	Detection of *H. pylori* antigen in stool
Results	Qualitative	Qualitative
Specimen Required	1. Stool	1. Stool
Technology	Lateral flow chromatography	Enzyme-linked immunoassay
Level of skill required	Laboratory Technician	Laboratory Technician
Assay steps	1. Dilute specimen in Sample Diluent 2. Add diluted specimen to test port 3. Incubate at 20-26 C for 5 minutes 4. Read results visually	1. Dilute specimen in Sample Diluent 2. Add diluted specimen to test well 3. Incubate at 22-27 C for 60 minutes 4. Wash test well 5. Add Conjugate Reagent 6. Add Substrate Reagent 7. Incubate at 22-27 C for 10 minutes 8. Add Stop Solution 9. Read results using spectrophotometer
End point	Visual color line	Color change, change in optical density of solution
Interpretation of test result	Positive = pink-red line Negative = no line	Positive = OD $\geq$ 0.120 at $A_{450/630}$ nm or $\geq$ 0.160 at A_{450} nm Negative = OD $\leq$ 0.100 at $A_{450/630}$ nm or < 0.140 at A_{450} nm

B. Device Components:

1. Test Devices: lateral flow membrane strips impregnated with monoclonal anti-*H. pylori* as the capture antibody, red latex-conjugated detector antibody. The strips are enclosed in a plastic case with a window.
2. Positive Control: a dilute suspension of inactivated *H. pylori* in a buffered solution containing <0.1% sodium azide as a preservative.
3. Specimen Diluent: a buffered salt solution containing <0.1% sodium azide as a preservative.

C. Principle of the Test:

ImmunoCard STAT! HpSA uses capture solid phase technology to detect the presence of antigen in test specimens.

To perform the test, patient stool is added to the Sample Diluent using the applicator stick that is part of the Sample Diluent Vial. The diluted stool sample (approximately a 1 in 10 dilution) is dispensed through the tip of the Sample Diluent Vial into the round sample window of the device. *H. pylori* antigen, if present in the diluted sample, binds to the detector antibody-latex conjugate as the sample moves through the device. The capture monoclonal antibody, which is bound to the assay membrane at reading window, binds the antigen-antibody-latex complex and yields a visible pink-red line. When no antigen is present, no complex is formed and no pink-red line will appear at the test position of the central window.

A control line, appearing at the control position in the test window, shows whether adequate flow has occurred through the device during a test run. The control line is a protein of nonmammalian origin.

Blue latex particles conjugated with a monoclonal antibody to this protein co-migrate with the latex-bound detector antibody during the incubation step. A blue line at the control position on the device should be present each time a specimen or control is tested. If no blue control line is seen, the test is considered invalid.

D. Contraindications, precautions, Warnings:

There are no known contraindications for ImmunoCard STAT! HpSA. See product labeling for precautions and limitations of for the use of this product as an in vitro diagnostic device.

MARKETING HISTORY:

ImmunoCard STAT! HpSA has been marketed since 2002 outside the United States. It is currently marketed in the European Union, in Japan and China. It has been the subject of several comparative studies conducted outside of the United States. (5-9)

ADVERSE EFFECTS OF THE DEVICE ON HEALTH:

There are no potential adverse effects of health associated with the use of this in vitro diagnostic device. The diagnosis of *H. pylori* infection is made on the clinical symptoms of the patient and confirmed through tests performed on isolated tissues, serum, urine or stool specimens. Conventional in vitro diagnostic methods for confirming *H pylori* infection include:

1) ^{13}C or ^{14}C-labeled urea breath test to detect ^{13}C or ^{14}C-labeled CO_2 expired in air as a result of *H. pylori* urease activity
2) Serology to detect circulating *H. pylori* IgG antibody in serum or whole blood
3) Stool assay for the detection of bacterial antigen

SUBSTANTIAL EQUIVALENCE:

Comparative studies: Four independent laboraories tested specimens in parallel with ImmunoCard STAT! HpSA and a reference ELISA in vitro diagnostic method, Premier Platinum HpSA (Meridian Bioscience, Inc, Cincinnati, OH). Some samples giving discordant results between the two assays were sent to and evaluated by a reference laboratory. The results of the parallel tests are given below. Corrected results are calculated following investigation of discordant samples by the referee laboratory.

	Initial Trial Results	Corrected Results
Total samples tested	457	457*
Concordant test results	433	436
Positive samples	102	105
Negative samples	331	331
Discordant test results	21	20
Premier +, ImmunoCard -	6	6
Premier -, ImmunoCard +	15	14
Indeterminant	3	1
Premier Equivocal, ImmunoCard +	2	1
Premier Equivocal, ImmunoCard -	1	0
% correlation	95%	N/A

* Two discordant samples were QNS for follow up analysis.

The lower limit of detection of this assay is 64 ng/mL in tests with sonicated antigen prepared from *H. pylori* strain TV1970. This limit does not vary from formed (solid) to semi-solid stool.

Clinical studies: Stool samples from 227 consecutive dyspeptic patients, who were not using acid suppressant therapy or antibiotics, and who were referred for endoscopy were tested with ImmunoCard STAT! HpSA. Biopsy specimens were taken for histology, rapid urease test and culture. Patients were defined as infected with *H. pylori* if histology and urease tests were positive, or if culture was positive. Eighty five of the 227 patients were found *H. pylori* positive. The results are summarized in the following table.

Diagnostic accuracy of ImmunoCard STAT! HpSA before and after *H. pylori* eradication treatment.

	H. pylori status by endoscopy/biopsy/gold standard		
	True Positive	True Negative	Total
IC STAT! HpSA +	77	12	89
IC STAT! HpSA -	8	130	138
Total	85	142	227
Estimated clinical sensitivity (95% CI)	90.6% (84.9 to 97.1%)		
Estimated clinical specificity (95% CI)	91.5% (87.5 to 96.5%)		
Predictive value, positive test (95% CI)	86.5% (79.9 to 94.1%)		
Predictive value, negative test (95% CI)	94.2% (90.1 to 97.9%)		
Correlation (CI 95%)	91.2% (87.3 to 94.7%)		

Correlation of ImmunoCard STAT! HpSA test results with eradication treatment

	H. pylori status by endoscopy/biopsy/gold standard		
	True Positive	True Negative	Total
IC STAT! HpSA +	21	0	21
IC STAT! HpSA -	1	63	64
Total	22	63	85
Estimated clinical sensitivity (95% CI)	95.4% (86.0 to 100%)		
Estimated clinical specificity (95% CI)	100%		
Predictive value, positive test (95% CI)	100%		
Predictive value, negative test (95% CI)	98.4% (94.5 to 100%)		
Correlation (CI 95%)	98.8% (96.8 to 100%)		

REPRODUCIBILITY

The reproducibility of ImmunoCard STAT! HpSA was determined with known negative (n = 5) and positive (n = 5) samples), that were coded and randomly sorted to prevent their identities. Two of the five positive samples were near the limit of detection for the assay. The reproducibility samples were tested on three consecutive days by three independent test sites. Intra-assay and interassay reproducibility was 100%.

			Referee (MBI)			Clinical Site # 1			Clinical Site # 2			Clinical Site # 3		
Sample Status	Premier OD reading	IC STAT! graded reading *	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day	Day 2	Day 3
Neg	0.017	0	0	0	0	0	0	0	0	0	0	0	0	0
Pos	0.737	4/5	+	+	+	+	+	+	+	+	+	+	+	+
Neg	0.016	0	0	0	0	0	0	0	0	0	0	0	0	0
Pos	1.140	7	+	+	+	+	+	+	+	+	+	+	+	+
Neg	0.028	0	0	0	0	0	0	0	0	0	0	0	0	0
Low Pos	1.442	1	+	+	+	w +	w +	w +	+	w +	+	+	+	+
Neg	0.042	0	0	0	0	0	0		0	0	0	0	0	0
Low Pos	1.041	2	+	+	+	+	w +	+	+	+	+	+	+	+
Pos	1.493	5	+	+	+	+	+	+	+	+	+	+	+	+
Neg	0.058	0	0	0	0	0	0	0	0	0	0	0	0	0
Pos Cont	2.309	N/A	+	+	+	+	+	+	+	+	+	+	+	+
Neg Cont	0.034	N/A	0	0	0	0	0	0	0	0	0	0	0	0

* The signal intensity (strength) of a positive reaction in ImmunoCard STAT! will not necessarily correlate with the OD value obtained in Premier Platinum HpSA EIA.

Legend: 0 = negative, 1-10 = semiquantitative scoring scale used in the interpretation of ImmunoCard STAT! positive test results. (A value was assigned to the intensity of color in the Test Line, where 1 is the weakest visible positive reaction and 10 is the strongest. A 4/5 means the reaction fell between a grade of 4 and a grade of 5.) w = weak (correlates with a semiquantitative reaction grade of +/-, 1 or 2)

ASSAY SPECIFICITY

The specificity of ImmunoCard STAT! HpSA was tested utilizing the following bacterial, viral and yeast strains. Positive and negative stools were spiked with $\geq$ 1 X 10^8 bacteria or yeast. None of the microorganisms tested yielded a positive result in the negative stool or interfered with detection of the positive stool. Both the negative and positive stool was positive when spiked with *Helicobacter pylori* strain 43504.

Adenovirus Type 2
Adenovirus Type 40
Coxsackie Type B1
Coxsackie Type B6
Echovirus Type 22
Feline calicivirus
Rotavirus

Aeromonas hydrophila
Campylobacter coli

Campylobacter jejuni
Candida albicans
Citrobacter freundii
Clostridium perfringens
Clostridium difficile (2)
Enterobacter cloacae
Enterococcus faecalis (2)
E. coli (2)
E. coli 0157:H7 (2)
E. fergusonii
Helicobacter felis
Klebsiella pneumoniae
Proteus vulgaris
Pseudomonas aeruginosa
Salmonella dublin
Salmonella (Group B)
Salmonella hilversum
Salmonella minnesota
Salmonella typhimurium
Staphylococcus aureus
Staphylococcus aureus (Cowan I)
Staphylococcus epidermidis
Serratia liquifaciens
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Shigella sonnei
Yersinia enterocolitica

Borrelia burgdorferi (Stool inoculated with antigen protein to a final conc. of 32 ug/mL)

TESTS FOR INTERFERING SUBSTANCES

The following substances were found to have no effect on results when present in stool at the concentrations indicated.

Tums® Antiacid (5 mg/mL)
Tagamet® (5 mg/mL)
Prilosec® (5 mg/mL)
Mylanta® Antacid (1:20)
Pepto-Bismol® (1:20)
Barium sulfate (5%)
Whole Blood (50%)
Leukocytes (50%)
Mucin (3.4%)
Stearic acid/palmitic acid (fecal fat) (4%)
Hemoglobin (tarry stool) (12.5%)

BIBLIOGRAPHY:

(1) Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984:1:1311-14.

(2) Dunn BE, Cohen H, Blaser MJ. *Helicobacter pylori*. Clin Miocobiol Reviews, 1997;10:720-41.

(4) Vaira D, Malferthainer P, Megraaud F, et al. Diagnosis of Helicobacter pylori infection with a new noninvasive antigen-based assay. Lancet 1999:345:30-3.

(5) Graham D. Helicobacter pylori: Its epidemiology and its role in duodenal disease. J Gastroenterol, 1991:4:105-13.

(6) Calvet K, Quesada M, Rosello M, et al. Stool antigen for the ddiagnosis of Helicobacter pylori infection in cirrohsis: comparative usefulness of three methods. Aliment Pharmacol Ther 2003;12:727-31.

(6) Calvet X, Salceda F, Sanfeliu I, et al. Testing a new in-office test for determination of faecal Helicobacter pylori antigen. Med Clin (Barc) 202;118:126-9.

(7) Antos D, Konstantopoulos N, Crone J, Koletzko S. Evaluation of a novel rapid one-step monoclonal enzyme immunoassay for detection of H. pylori antigen in stool in children. Abstract presented at the 26th Annual Meeting European Society for Pediatric Gastroenterology, Hepatology and Nutrition. Prague, Czech Republic, June 2003.

(8) Perna F, Tampieri A, Rici C et al. Evaluation of a new rapid one step stool antigen test for Helicobacter pylori (HP) infection diagnosis. Abstracted presented at the XV International Workshop Gastrointestinal Pathology and Helicobacter, Athens, Greece, September 11-14, 2002.

(9) Lebdolter A, Wolle K, Wex T et al. Evaluation of a novel rapid H. pylori stool antigen test: Is a reliable now possible in the doctor's office? Abstract presented at the Digestive Disease Week, Orlando Florida, May 2003.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

DEC - 5 2003

Ms. Susan Rolih
Vice President, Regulatory Affairs and Quality Assurance
Official Correspondent
Meridian Bioscience, Inc.
3471 River Hills Drive
Cincinnati, OH 45244

Re: k032222
Trade/Device Name: ImmunoCard *STAT!* HpSA
Regulation Number: 21 CFR 866.3110
Regulation Name: Campylobacter Fetus Serological Reagents
Regulatory Class: Class I
Product Code: LYR
Dated: October 24, 2003
Received: October 27, 2003

Dear Ms. Rolih:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 594-3084. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): K032222

Device Name: ImmunoCard *STAT!* HpSA

Indications For Use: ImmunoCard *STAT!* HpSA is a rapid in vitro qualitative assay for the detection of Helicobacter pylori antigen (HpSA) in human stool. The stool antigen detection is intended to aid in the diagnosis of *H. pylori* infection and to demonstrate loss of *H. pylori* stool antigen following treatment. Conventional medical practice recommends that testing by any method to confirm the loss of antigen be done at least four weeks following completion of therapy.

Prescription Use ✓ No__ AND/OR Over-The-Counter Use __No___
(Part 21 CFR 801 Subpart D) (21 CFR 807 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off

Office of In Vitro Diagnostic Device
Evaluation and Safety

K032222